Serial No.: 09/872,769
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## REMARKS

Claims 1-10 are pending. Claims 1, 4-5 have been amended to recite with more particularity the antiproliferative agents used in the methods of the invention. The claims have support in the specification at p. 5, lines 4-17. Claim 6 has been amended to correct the reference to "antiproliferative agent." New claim 14 has been added, and has support in Example 1, pp. 6-8. Changes to the claims are shown in the Appendix entitled "MARKED UP VERSION TO SHOW CHANGES MADE." An additional appendix of the pending claims is attached for the Examiner's convenience. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the reasons that follow.

**Election/Restrictions**

The claims have been restricted to two groups, as follows:

I. Claims 1-10, directed to a method of treatment; and

II. Claims 11-13, directed to a composition.

Applicant hereby elects group I.

**Rejection under 35 U.S.C. § 112**

Claim 13 is rejected under 35 U.S.C. 112 as indefinite. Claim 13 is also rejected under 35 U.S.C. 101 as being an improper process claim. Without admitting the propriety of the rejection, Applicant has canceled the claim. Applicant respectfully requests that the rejections be withdrawn.

**Rejection under 35 U.S.C. § 102**

Claims 1 and 4-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Barnett et al. ("Barnett,", U.S. Pat. No. 6,103,487). Applicants respectfully traverse.

Claims 1 and 4-11 are directed to methods of treatment of a host with a cellular proliferative disease. The methods include contacting the host with a hexitol and an antiproliferative agent. The hexitol and the antiproliferative agent are each provided in an amount sufficient to modulate the cellular proliferative disease.

"Anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference... There must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of invention." Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001.

Barnett teaches the use of hexitol as components of excipients, in "partial esters derived from fatty acids and a hexitol ..." or "partial esters derived from fatty acids and hexitol anhydrides ...." Barnett does not teach that such excipients can modulate a proliferative disease or that such excipients are provided in amounts sufficient to modulate a cellular proliferative disease. Barnett also does not teach a method wherein the disease modulation is greater than modulation by the antiproliferative agent alone. Because Barnett does not teach all elements of the claims, Barnett does not anticipate the claims. Applicants respectfully request that the rejection be withdrawn.

**Rejection under 35 U.S.C. § 103**

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis (U.S. Pat. No. 4,797,388, "Francis") further in view of Levin et al. (Cancer Chemother. Pharmacol. 8:125-31 (1982), "Levin"). Applicants respectfully traverse.

Francis teaches pharmaceutical compositions containing galactitol as a carrier for a therapeutic anti-tumor agent. The anti-tumor agent may be cisplatin. Francis further teaches that use of galactitol enhances stability of the therapeutic agent and allows faster reconstitution in water.

Levin teaches that the antitumor activity of hexitol epoxides may be enhanced by drug combination therapies. Levin further teaches that the combination of dianhydrogalactitol (DAG) and BCNU in treating IC glioma 26 (brain neoplasm) was curative in 85-100% of animals while treatment with either DAG or BCNU alone gave limited survival.

The claims are directed to methods of treatment comprising contacting a host with a hexitol and an antiproliferative agent. The hexitol and the antiproliferative agent are each provided in amounts sufficient to modulate the cellular proliferative disease. Furthermore, claim 1 has been amended to exclude alkylating agents, under which BCNU falls, from the

claimed antiproliferative agents. The hexitol may comprise DAG or a DAG analog. The antiproliferative agent may comprise cisplatin.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must demonstrate three criteria. First, the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; second, the prior art must provide one of ordinary skill with a reasonable expectation of success; and finally, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. M.P.E.P. § 2143.

Francis does not teach or suggest the use of a hexitol, nor that the hexitol modulates a cellular proliferative disease. Hexitols are defined as the group having the chemical structure as depicted in Figure 1 (see p. 4, lines 13-15). Francis also does not teach a method wherein the hexitol comprises DAG or a DAG analog. Nor does Francis teach or suggest a method wherein the disease modulation is greater than modulation by the antiproliferative agent alone.

Levin does not teach the claimed combination. Levin teaches the use of BCNU, an alkylating agent. Levin does not teach or suggest a method wherein the antiproliferative agent is an antimetabolite, a structural protein agent, an agent that affects protein synthesis, an antibiotic, a hormone antagonist, an intercalating agent, a topoisomerase inhibitor or a metal coordination complexes, as recited in the amended claim. Nor does Levin teach or suggest a method wherein the disease modulation is greater than modulation by the antiproliferative agent alone.

To the extent that the Examiner may be relying on an "obvious to try" theory of obviousness, Applicants remind the Examiner that a rejection based on an "obvious to try" criterion is not proper under 35 U.S.C. § 103. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See also *The Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923 (Fed. Cir. 1990). "An `obvious to try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the

disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *The Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1928 (CAFC 1990).

In the present case, Levin teaches merely that DAG combined with BCNU enhances the effect seen by either agent alone in treating a brain neoplasm. Although the reference suggests that further combination therapies may be useful, it fails to disclose any of the claimed specific drug combinations. Thus, it merely operates as an invitation to experiment further.

Francis does not cure the defects of Levin. First, Francis teaches the use of galactitol, not the use of a hexitol as defined in the present application. Thus, the two references do not teach each and every limitation of the claims. Additionally, Francis uses galactitol as an excipient and does not teach the use galactitol as an active agent that can itself modulate a cellular proliferative disease. One skilled in the art would not be motivated by either art reference to modify the combination taught by Levin to obtain the claimed invention.

Applicants respectfully submit that the claims are now in condition for allowance and an early notification of such is solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Applicants respectfully request that the Examiner call the undersigned attorney.

Respectfully submitted,

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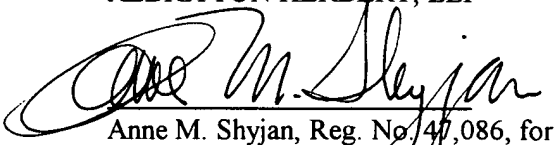

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**MARKED UP VERSION TO SHOW CHANGES MADE**

1. (Amended) A method of treatment of a host with a cellular proliferative disease, comprising contacting said host with a hexitol and an antiproliferative agent, each in an amount sufficient to modulate said cellular proliferative disease, wherein said antiproliferative agent is selected from the group consisting of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes.

4. (Amended) The method according to claim 1 wherein said antiproliferative agent comprises an intercalating agent [that interacts with nucleic acids] .

5. (Amended) The method according to claim 1 wherein said antiproliferative agent comprises [an alkylating agent, an intercalating agent,] a metal coordination complex[, a pyrimidine nucleoside, a purine, an inhibitor of nucleic acid associated enzymes, or an inhibitor of nucleic acid associated proteins].

6. (Amended) The method according to claim 1 wherein said antiproliferative agent comprises cisplatin.

## APPENDIX: PENDING CLAIMS

1. (Amended) A method of treatment of a host with a cellular proliferative disease, comprising contacting said host with a hexitol and an antiproliferative agent, each in an amount sufficient to modulate said cellular proliferative disease, wherein said antiproliferative agent is selected from the group consisting of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes.

2. The method according to claim 1, wherein said hexitol comprises dianhydrogalactitol (Dianhydrodulcitol; Dulcitol diepoxide; DAD; DAG; 5,6-Diepoxydulcitol; 1,2:5,6-Dianhydrodulcitol; 1,2:5,6-Dianhydrogalactitol; 1,2:5,6-Diepoxydulcitol).

3. The method according to claim 1, wherein said hexitol comprises a dianhydrogalactitol analog.

4. (Amended) The method according to claim 1 wherein said antiproliferative agent comprises an intercalating agent.

5. (Amended) The method according to claim 1 wherein said antiproliferative agent comprises a metal coordination complex.

6. (Amended) The method according to claim 1 wherein said antiproliferative agent comprises cisplatin.

7. A method according to claim 1 wherein said hexitol is administered before the administration of said antiproliferative agent.

8. A method according to claim 1 when said hexitol is administered during the administration of said antiproliferative agent.

9. A method according to claim 1 wherein said hexitol is administered after the administration of said antiproliferative agent.

10. The method of claim 1 wherein the modulation of said disease with said composition is greater than that for said antiproliferative agent alone.

14. (New) A method according to claim 1 wherein said cellular proliferative disease is a solid tumor.